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Profiling the subjective effects of Δ9-tetrahydrocannabinol using visual analogue scales

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Abstract

The subjective effects of cannabis and its main psychoactive component Δ^9-tetrahydrocannabinol (THC) have played an important part in determining the therapeutic potential of cannabinoid agonists and antagonists. The effects mainly consist of feeling high, changes in perception, feelings of relaxation and occasionally dysphoric reactions. These effects are captured by two of the most frequently used visual analogue scales (VASs) in clinical (pharmacologic) research to measure subjective effects: VAS Bond and Lader (alertness, calmness and mood) and VAS Bowdle (psychedelic effects). In this analysis, the effects of THC on these VASs were compared within a total of 217 subjects who participated in 10 different studies. Not surprisingly, the item feeling high was found to be the best predictor for the effect of THC. Three separate clusters that describe the spectrum of subjective effects of THC were identified using different statistical methods, consisting of VAS "time", "thoughts" and "high" ("perception"), VAS "drowsy", "muzzy", "mentally slow" and "dreamy" ("relaxation") and VAS "voices", "meaning" and "suspicious" ("dysphoria"). These results provide experimental evidence that THC can evoke different classes of effects. These distinct subjective clusters could represent effects on various systems in the brain, which can be used to further differentiate the involvement of endocannabinoid systems in health and disease. *Copyright © 2014 John Wiley & Sons, Ltd.*

Introduction

Cannabis is best known as a recreational drug that is widely used throughout the world, although its use is illegal in most countries. The main psychoactive component of cannabis is Δ^9-tetrahydrocannabinol (THC), which is an agonist at cannabinoid CB_1 and CB_2 receptors. Both cannabis and THC have been used in preclinical and clinical research to investigate the effects on pain (reviewed by Lynch and Campbell, 2011), food intake (reviewed by Berry and Mechoulam, 2002), pain and spasticity in multiple sclerosis (reviewed by Karst *et al*., 2010; Zajicek and Apostu, 2011) and as models of psychosis (D'Souza *et al*., 2004; Kleinloog *et al*., 2012; Liem-Moolenaar *et al*., 2010). Alternatively, CB_1-antagonists (e.g. rimonabant) have been shown to block the anti-nociceptive effects of THC (Compton *et al*., 1996), reduce food intake and facilitate weight loss (van Gaal *et al*., 2005), and there is literature that suggests a relation between CB_1-antagonism and the development of multiple sclerosis (van Oosten *et al*., 2004) and improvement of symptoms in schizophrenia (Kelly *et al*., 2011). Many of these investigative indications have been inspired by the subjective effect profile of cannabis and THC. These subjective effects, which are largely attributable to THC, can be quite diverse. The main effect is a "high" feeling, which is described by Ashton (2001, p. 104) as "a feeling of intoxication, with decreased anxiety, alertness, depression and tension and increased sociability". Less frequently, there can also be effects that are reminiscent of psychosis, like distorted perceptions of colour, space and time. Other effects are impairments of reaction time, short-term memory and motor coordination. Dysphoric reactions, described by Ashton (2001) as "anxiety and panic, paranoia and psychosis" can also occur. In addition, cannabis can induce feelings of appetite ("munchies"). The factors that determine the intensity of each of these effects have not been investigated in detail, but the subjective effects of THC seem to differ among users, and probably also between occasions of use or doses and modes of administration. There are many ways in which the (subjective) effects of cannabis and THC can be measured. In a review by Zuurman *et al.* (2009) feeling high was shown to be the most sensitive central nervous system (CNS) biomarker for the effects of cannabis, essentially irrespective of how this was measured. A frequently used tool to measure subjective feelings is the visual analogue scale (VAS). A VAS typically consists of a 100 mm long line, with two extremes on the sides. A subject is asked to indicate his or her current feelings somewhere on the line between the two extremes. Bowdle *et al.* (1998) described a composite scale for psychedelic effects (hereafter VAS Bowdle, see Table 1), consisting of 13 questions with the extremes of "not at all" and "extremely", and validated this scale in a group of healthy volunteers who received ketamine. Zuurman *et al.* (2008) used the VAS Bowdle to measure the subjective effects of THC. Based on cluster analysis and factor analysis, they suggest the use of two distinct composite scales, which were classified as "internal perception" (VAS "reality", "voices", "meaning", "suspicious" and "anxious") and "external perception" (VAS "body", "surroundings", "time", "thoughts", "colours" and "sounds"), in addition to the item "high" (Zuurman *et al.*, 2008). This same study also reported dose-related effects on subjective alertness, which were assessed using the VAS described by Bond and Lader (1974). These authors identified 16 combinations of two subjective states (Table 1), combined in clusters of alertness (VAS "drowsy", "feeble", "muzzy", "clumsy", "lethargic", "mentally slow", "dreamy", "incompetent" and "bored"), calmness (VAS "calm" and "relaxed") and mood (VAS "contented", "tranquil", "happy", "amicable" and "gregarious"), based on a principal component analysis (PCA) on response in a group of healthy volunteers, without intervention. Norris (1971) had previously subdivided these 16 items into four categories of four items each, based on a conceptual framework. These categories are "mental sedation or intellectual impairment" (items "drowsy", "muzzy", "mentally slow" and "dreamy"), "physical sedation or bodily impairments" (items "feeble", "clumsy", "lethargic" and "incompetent"), "tranquillization or calming effects" (items "calm", "contented", "tranquil" and "relaxed") and "other types of feelings or attitudes" (items "happy", "amicable", "bored" and "gregarious").

In combination, the 13 VAS described by Bowdle and the 16 scales used by Bond and Lader cover most of the subjective effects of cannabis and THC that were summarized by Ashton (2001), with the exception of the effects on appetite. The subjective effects of cannabis and THC are relevant, considering their putative therapeutic potential and pathophysiological significance. The aim of the current analysis is to identify distinct profiles within the spectrum of characteristic subjective effects of THC as measured using well-known sets of VAS. Such distinct effect profiles could provide quantitative information on different neurophysiological effects of THC, and on different sensitivities of individuals to such effects. When these profiles are combined in composite scales, they can be used in the design and interpretation of studies assessing the effect of THC or cannabis and to improve our understanding of the endocannabinoid system in health and disease. For example, the relation between these subjective effects and personality or genetic constitution could be examined (van Winkel and Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011), or the relationship between activation of certain brain regions in neuroimaging studies and subjective response patterns of THC or cannabis (e.g. Atakan *et al.*, 2013). Individual VAS items are compared on sensitivity to the effects of THC, including a possible dose–response relationship. Also, different multivariate techniques were employed to examine if the clustering of different VAS items elicited distinct response patterns.

Methods

Data collection

Data from 10 studies performed by the Centre for Human Drug Research (CHDR) in which THC was administered to a total of 217 healthy volunteers were selected to perform an exploratory analysis on the measurements of the subjective effects of THC. The time points and measurements of VAS Bond and Lader and VAS Bowdle, as well as the time points of drug administration and administered dose were used for the analysis. All the studies had a randomized, cross-over, placebo-controlled design and were approved by the local Ethics Committee. Some studies were interaction studies, but only the treatment arms that involved administration of either THC alone or placebo alone were taken into account. An

Table 1. Description of visual analogue scales (VASs)

VAS Bowdle

Item	Name	Full description
1	Body	My body or body parts seemed to change their shape or position.
2	Surroundings	My surroundings seemed to change in size, depth, or shape.
3	Time	The passing of time was altered.
4	Reality	I had feelings of unreality.
5	Thoughts	It was difficult to control my thoughts.
6	Colours	The intensity of colours changed.
7	Sound	The intensity of sound changed.
8	Voices	I heard voices or sounds that were not real.
9	Meaning	I had the idea that events, objects, or other people had particular meaning that was specific for me.
10	Suspicious	I had suspicious ideas or the belief that others were against me.
11	High	I felt high
12	Drowsy	I felt drowsy.
13	Anxious	I felt anxious.

VAS Bond and Lader

Item	Name	First extreme	Second extreme
1	Drowsy	Alert	Drowsy
2	Calm	Calm	Excited
3	Feeble	Strong	Feeble
4	Muzzy	Muzzy	Clear-headed
5	Clumsy	Well-coordinated	Clumsy
6	Lethargic	Lethargic	Energetic
7	Contented	Contented	Discontented
8	Tranquil	Troubled	Tranquil
9	Mentally slow	Mentally slow	Quick witted
10	Relaxed	Tense	Relaxed
11	Dreamy	Attentive	Dreamy
12	Incompetent	Incompetent	Proficient
13	Happy	Happy	Sad
14	Amicable	Antagonistic	Amicable
15	Bored	Interested	Bored
16	Gregarious	Withdrawn	Gregarious

overview of the studies and their references is provided in Table 2. All healthy volunteers who participated in the studies were mild cannabis users, defined as a frequency of cannabis use of maximum once a week in the past year.

THC challenge

In nine out of 10 studies (94.5% of subjects) purified THC was inhaled using the Volcano™ vaporizer (Storz-Bickel, Tuttlingen, Germany). This method is described in more detail by Zuurman *et al.* (2008). In all these studies, several administrations were given during a study day to prolong the effect of THC. This was typically an increasing dose (2 mg, 4 mg, 6 mg) with 60 to 90 minute intervals, although the actual dosing regimen was different throughout the studies (see Table 2). One study used single doses of oral or sublingual tablets of purified THC. This study was included as a check of the notion that THC effects are determined by individual sensitivity and brain concentrations, and not by administration route.

Table 2. Overview of original studies

Reference	*N*	Doses	Interval	VAS timepoints
Bossong *et al.*, 2009	7	8 mg inhalation	Not available	7, 12, 17, 32 and 105 minutes after dose
van Hell *et al.*, 2011	26	6 + 1 + 1 + 1 mg	30 minutes	27 and 34 minutes after first dose
Kleinloog *et al.*, 2012	49	2 + 4 + 6 mg	90 minutes	13, 25, 33 and 64 minutes after each dose
Klumpers *et al.*, 2012a	12	5, 6.5 or 8 mg	Oral	19, 36, 51, 65, 95 minutes after dose
Klumpers *et al.*, 2012b	22	2 + 6 + 6 mg	90 minutes	29, 59 and 83 minutes after each dose
Klumpers *et al.*, 2013a	30	2 + 4 + 6 + 6 mg	60 minutes	23 and 41 minutes after each dose
Klumpers *et al.*, 2013b	34	5 × 4 mg	≥ 150 minutes	10, 24 and 115 minutes after each dose
Liem-Moolenaar *et al.*, 2010	37	2 + 4 + 6 mg	90 minutes	22, 34 and 61 minutes after each dose
Zuurman *et al.*, 2008	12	2 + 4 + 6 + 8 mg	90 minutes	22 and 47 minutes after each dose
Zuurman *et al.*, 2010	36	2 + 4 + 6 + 6 mg	60 minutes	23 and 41 minutes after each dose

Quality control

Prior to the analysis, a visual quality check of the available data was performed. In this regard, for each VAS item the data of the placebo condition from different studies were presented as boxplots. As no subjective effects are expected during the placebo condition, the scores for the items of the VAS Bond and Lader were expected to be distributed around the middle and the scores for the items of the VAS Bowdle close to a score of 0 mm. A few studies showed a distribution during the placebo condition that was distinctly different from the other studies (based on visual comparison), and these were excluded from further analysis.

Item sensitivity

Measurements performed in the first 60 minutes after THC administration were pooled to identify items that are sensitive to THC. Items that showed a significant difference between THC and placebo were selected for further analysis. A Kruskal–Wallis test was used as the distribution was not normal. A p-value of 0.05/29 (Bonferroni correction for number of VAS items) was considered significant.

Defining responders

Not all subjects showed a response on the VAS after administration of THC. Subjects were therefore classified as responder or non-responder for each individual VAS item. To make this classification, the distribution of observed scores for the overall placebo condition was examined, and the values within the 95% observation interval during placebo were considered indicative for the absence of a response. Conversely, subjects were considered a responder for a specific VAS item if they showed a response outside this 95% limit during any measurement in the THC condition.

Dose–response relationships

To determine possible dose–response relationships for the different VAS items that are sensitive for the effect of THC, the studies that used intrapulmonary administration of THC were selected. Most of these studies had a design where multiple doses of THC were administered on each study day, with a fixed time interval between administrations. As the times of measurements were different for each study, the maximum response after each administration was used. All individual studies were designed to include measurements around the expected maximum effect (T_{max}). Possible relationships were tested using a Kruskal–Wallis test and a p-value of $0.05/n$ (Bonferroni correction) was considered significant. Since most studies included several different consecutive doses on each individual study occasion, it was possible to assess a dose–response relationship, which was performed in two steps. Initially, only the first administration of THC during each study day was taken into account, which assured the absence of carry-over effects and tolerance. Subsequently, all administrations during each study day were considered if the dosing interval was at least 60 minutes, which covered more observations and a larger dose range. Both steps were repeated within subjects who were identified as responders.

Cluster selection

For the items that showed a significant dose–response relationship, different methods were applied to determine the combination of (weighted) items that could best describe "the subjective effect of THC". The combinations of items found with these different methods were then compared on their ability to predict the drug condition (THC or placebo). To find clusters within the dataset, multiple correspondence analysis (MCA), PCA, factor analysis (FA), k-means cluster analysis (KCA), hierarchical

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cluster analysis (HCA), variable clustering (VC) and discriminant analysis (DA) were used. Each technique has its own advantages and should more or less lead to the same conclusion if the clusters are the result of an underlying construct. The final cluster selection was based on what the different clustering methods have in common. MCA is an exploratory technique that uses logical indicators (true or false), which makes it more suitable for data that is not normally distributed or categorical (Greenacre, 2007). For MCA, the dataset was recoded into responders and non-responders, and the final item selection was based on the inertia of the items. PCA is the most commonly used tool in exploratory data analysis (Jolliffe, 2002). FA is a technique similar to PCA, but it only focuses on the variability that is shared with another item, whereas PCA takes all variability into account (Jolliffe, 2002). Both techniques can be applied to a dataset that is jointly normally distributed and are sensitive to the relative scaling of the original variables. PCA and FA were therefore performed using the maximum response in the THC condition, after a mean subtraction for all VAS items and log-transformation for VAS Bowdle items. KCA is a disjoint clustering method, in which all items are distributed within a pre-defined number of separated clusters to minimize within-cluster variability and maximize between-cluster variability (Hartigan and Wong, 1979). Within HCA and VC, clusters are organized to identify a hierarchical structure based on similarity between items, which is typically presented as a dendrogram (Jain *et al*., 1999). Linear stepwise DA is another method to find combinations of items that are able to predict the subjective effect of THC. For this analysis, the maximum response following intrapulmonary administration of THC was used to select items and the data from the study that was performed most recently were exclusively used for cross-validation. A stopping criterion of 0.1% improvement was used for forward and combined analysis and a stopping criterion of −0.5% improvement (either any improvement or a maximum of 0.5% worsening) for backward analysis.

Inverse predictive check

An inverse predictive check was performed for the individual items and the possible combinations of items to compare the probability to identify the original treatment. In this regard, predictive values were calculated for each individual VAS item, the clusters described by Bond and Lader (1974) and Zuurman *et al*. (2008), and the combinations of items found in the current analysis. The predictive value describes the chance that the score on a certain item (or combination of items) correctly identifies the given treatment (THC or placebo). As there are two possible outcomes (THC or placebo), the *a priori* predictive value is 50%. Again, the data from the study that was most recently performed were exclusively used for cross-validation.

Statistical software

The open source statistical software package R (version 2.14.0, www.r-project.org) was used for the analyses.

Results

Quality control

Based on a visual check of the distribution of scores under placebo conditions and prior to other evaluations, three studies [with a total of 74 (34.1%) subjects] were excluded from further analysis, based on the scores under placebo on all VAS items. One study showed a slightly different placebo profile compared with the other studies, which was a positron emission tomography (PET)-study with administration of [^{11}C]-raclopride and PET-measurements during THC administration in both study arms. It was decided to include the information from this study with the use of placebo correction.

Item sensitivity

VAS Bond and Lader items “contented”, “tranquil”, “happy”, “amicable” and “bored” were the only items that did not show a statistically significant different score between THC and placebo conditions (after Bonferroni correction). All these items are part of Bond and Lader’s “mood” cluster, with the exception of VAS “bored”.

Selection of responders

Table 2 shows the upper and lower limits of the 95% observation interval for VAS Bowdle and VAS Bond and Lader, respectively, during all placebo occasions. Individual scores outside of these limits during THC occasions were considered to be indicative of a drug response. The percentages of subjects who were classified as item responders after THC administration are presented per item.

Dose–response relationships

When taking into account all administrations and all subjects, VAS “drowsy”, “feeble”, “clumsy” and “dreamy” of Bond and Lader and all VAS Bowdle items except “voices” and “anxious” showed a significant dose − response relation using a p-value of 0.05/96 (Bonferroni correction for four times 24 items; the five items that did not differ significantly between placebo and THC were not taken along). The items that showed a significant dose − response relation for all administrations and all subjects were used for cluster selection. It should be noted that the dose interval (mostly between 60 and 90 minutes) is likely to have resulted in an accumulation of effect. The dose level of 8 mg is not included in the dose – response analysis, as only eight observations were available for this dose (compared to 150, 110, 118 and 101 observations for the other doses).

Multiple correspondence analysis

The outcome of the MCA is presented in Figure 1. The closer two data points are to one another, the more likely they are to show a response at the same time. Items that are relatively closer to the right side of the map are items that are more likely to show a response than items that are closer to the left side of the map. The relative inertia of the items is provided in Table 2. Inertia is a measure of how much the item contributes independent of other items (comparable to eigenvalues).

Principal component analysis (PCA) and factor analysis (FA)

Following parallel analysis, two components were selected for the varimax rotated PCA based on the observation of a "sharp break" in the scree plot. Another way of determining the optimal number of components is comparing the eigenvalues of the possible components in the dataset with those obtained from a random, simulated dataset of the same size. Using this approach, three components would have been selected. Figure 2 presents a map of the rotated PCA and the factor loadings are presented in Table 2. For FA (based on maximum likelihood), parallel analysis suggested the use of five factors, which are presented in Figure 3.

Cluster analysis

Within KCA, all items were assigned to one of three clusters. This technique gives no indication as to how well the variable fits into the cluster. Although items were scaled to

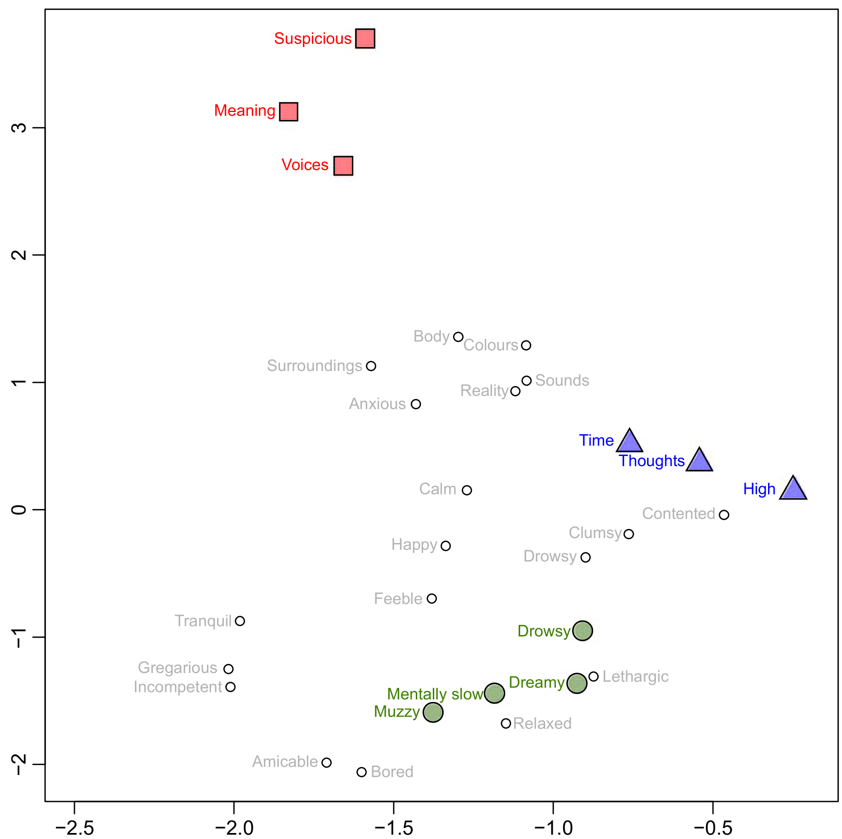

Figure 1. Map of multiple correspondence analysis (MCA). The final cluster selection based on all methods has been highlighted (red squares: dysphoria; blue triangles: perception; green circles: relaxation).

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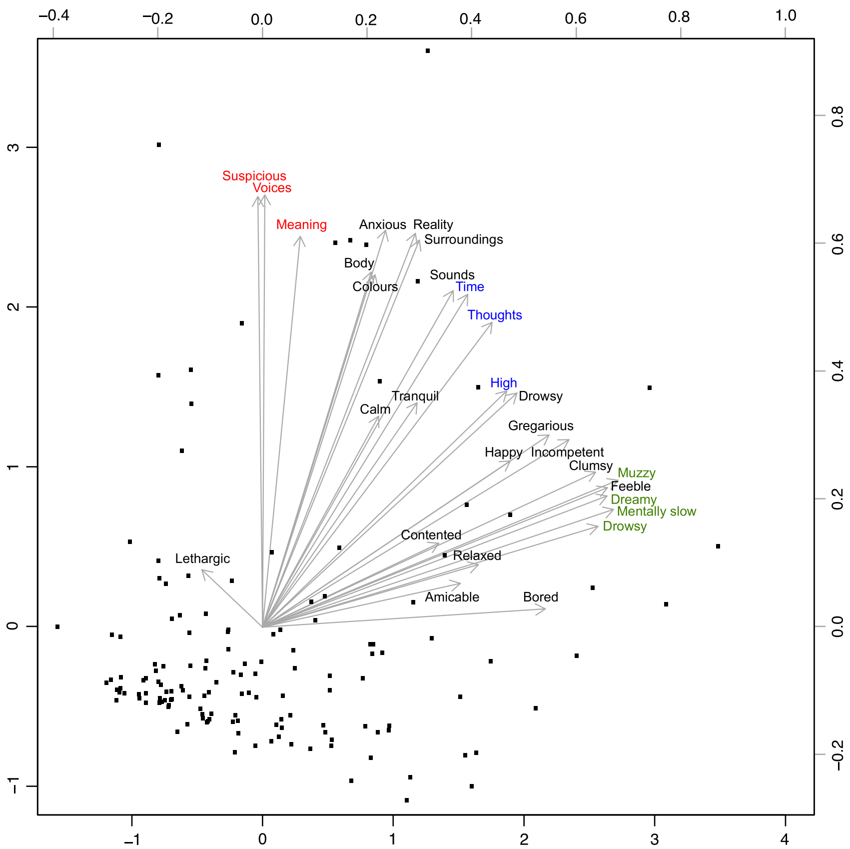

Figure 2. Plot of rotated principal component analysis (PCA) (green: relaxation; red: dysphoria; blue: perception).

allow for better comparison, all items of VAS Bond and Lader grouped into one cluster and VAS Bowdle items "surroundings", "colours", "sound" and "suspicious" were separated from the remaining items. The results of HCA are presented in Figure 4. Variable clustering had similar results. Because all these clustering methods will place all items within a cluster, the items that do not cluster consistently throughout the methods (e.g. item "drowsy" of VAS Bowdle) are likely irrelevant.

Discriminant analysis (DA)

Forward, backward and combined discriminant analyses were performed. The results from the combined DA were equal to the results of forward DA and are therefore not presented separately. Forward DA identified VAS "calm", "dreamy", "incompetent" and "high" as most predictive for the effect of THC and backward DA identified VAS "lethargic", "relaxed", "incompetent", "bored", "gregarious", "thoughts" and "high". As VAS "high" was expected to have a large impact on the outcomes, the analysis was repeated without this item, resulting in a combination of VAS "lethargic", "dreamy", "thoughts" and "colours" in case of forward DA and the same items together with VAS "sound" in case of backward DA.

Inverse predictive check

To calculate the predictive value of the different combinations of items, two methods were used: a composite (average) score of the items and a combination of the individual scores on the different items. Individually, VAS "high" has the best predictive value (83.6%), followed by VAS "thoughts" (77.1%), VAS "mentally slow" (75.8%) and VAS "time" (75.2%), as presented in Table 2. From the different combinations of items, only those found with DA resulted in a better predictive value as a composite scale.

Discussion

THC and cannabis have a rather broad range of effects, which can differ between subjects, doses and use circumstances. The effect patterns can give insight into the many different functions, therapeutic areas and diseases in which the cannabinoid system has been implicated. This analysis

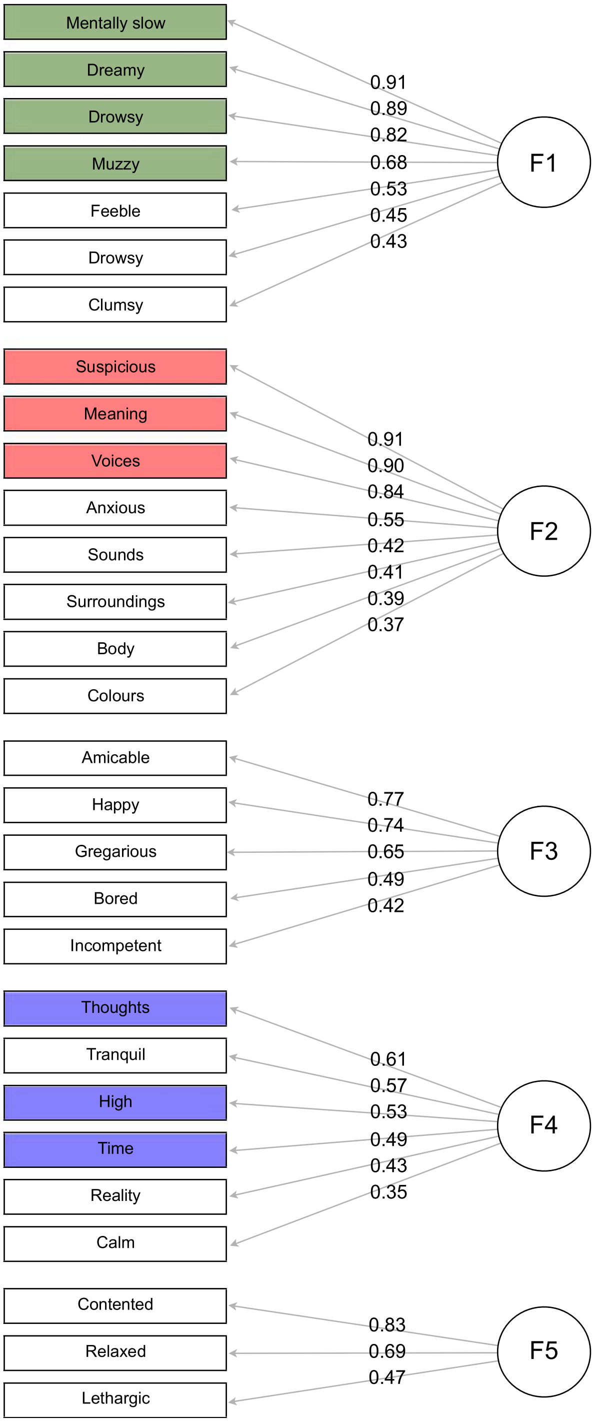

Figure 3. Overview of factor analysis (FA) (green: relaxation; red: dysphoria; blue: perception).

explored the characteristics of the scope of subjective effects of THC as measured on different VASs. As THC is the main component of cannabis and the elicited subjective effects of THC are comparable to the subjective effects of cannabis described in the literature, the findings might be applicable to cannabis. However, the other components of cannabis (i.e. cannabidiol) might distort the subjective effect patterns. It is important to note that different preparations of cannabis have different levels of THC and cannabidiol. The analysis examines the effects of THC in mild cannabis users. Results might be relevant to other groups of people (heavy users, non-users), although further research is needed.

VAS Bond and Lader and VAS Bowdle are frequently used in CNS drug research and capture most of the subjective effects that have been described with cannabis or THC. Not surprisingly, the analysis indicated that feeling high was the most predictive item for the effects of THC, which confirms the literature review of Zuurman *et al.* (2009) that showed a statistically significant "high" effect in 96% of cannabis studies. The other items that had high individual predictive values describe effects on time perception and cognitive functions (controlling of thoughts and mental slowness), which are also well known and frequent effects of cannabis and THC (Ashton, 2001). The items with high predictive values could be grouped into three distinct factors of effect. Table 3 presents an overview of the proposed composite scale that measures these factors.

The first common factor that was found using the different methods of cluster selection consists of VAS "time", "thoughts" and "high". VAS "colours" and "sound" showed a relation with this factor. Together, this factor can be described conceptually as a measure of feeling high and changes in perception ("perception"). All these items were a part of the cluster "external perception" as described by Zuurman *et al.* (2008), except "high" which was treated by Zuurman *et al.* (2008) as a separate cluster because of its predominance. This clustering of feeling high and the other items follows the description of the most typical THC effects by Ashton (2001).

VAS "drowsy" (from VAS Bond and Lader), "muzzy", "mentally slow" and "dreamy" constitute the second common factor. VAS "feeble" and "clumsy" showed a relation with this factor. All these items are included in the "alertness" clusters as described by Bond and Lader (1974). The main four items can be seen as mental aspects of sedation ("relaxation"), whereas the two related items are more physical aspects of sedation.

VAS "voices", "meaning" and "suspicious" are included in the third common factor within the effects of THC. These items may represent what Ashton (2001) describes as "dysphoric reactions" ("dysphoria"). Zuurman *et al.* (2008) included these items in the "internal perception"

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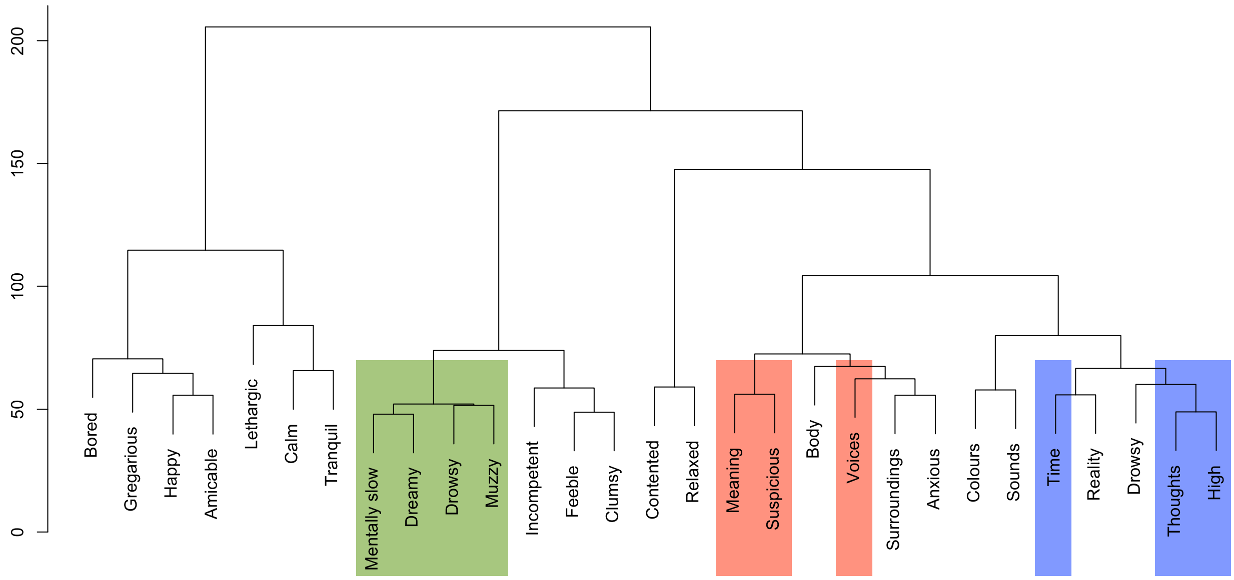

Figure 4. Overview of hierarchical cluster analysis (HCA). The final cluster selection based on all methods has been highlighted (green: relaxation; red: dysphoria; blue: perception).

cluster. Not many subjects show an effect on these items, but if these scales are affected, the effects seem to be clear. Even though this cluster of items does not seem highly predictive of the effect of THC, this aspect might correlate with other important predictors for the effect of THC such as the occurrence of adverse events. Henquet *et al.* (2005) suggest these "dysphoric reactions" could also reflect a predisposition for the development of psychosis.

Within the PCA, these three factors ("perception", "relaxation" and "dysphoria") were shown to represent two principal components. The majority of the variation was explained by "relaxation" (aligned with the horizontal component in Figure 2). The remaining variation could be explained by "dysphoria" (aligned with the vertical component in Figure 2), which appears to be the opposite of mental relaxation. The "perception" effects (the more "typical" effects of THC) were not a part of the two components, but rather seem to represent a separate component that is a vector of the other two clusters and therefore represents the main underlying effect. As described earlier, another way of determining the number of components would have resulted in three components.

The items that did not show a significant difference between THC and placebo are a part of the "mood" cluster in the VAS Bond and Lader, with the exception of VAS "bored" (a scale that does seem to relate to mood). This would suggest that THC does not affect mood in a stricter sense, which is consistent with the review by Zuurman *et al.* (2009). The effect of THC on appetite is not measured by VAS Bond and Lader or VAS Bowdle and therefore not taken along in the current analysis. Given the relevance of THC (and the endocannabinoid system) on appetite (Farrimond *et al.*, 2011), it would have been interesting to observe how additional VAS scales of hunger and appetite would have behaved in relation with the other clusters. For use in future studies, the authors would recommend the addition of scales for hunger and appetite.

A more complete assessment of the different effect dimensions of THC could aid in the exploration of the various pharmacological and physiologic aspects of cannabinoid systems, in health and disease. For example, the interactions of different constituents of cannabis (i.e. THC and cannabidiol) could be disentangled, by measuring the effects of each component and different combinations of components (Bhattacharyya *et al.*, 2010). Also, the effect profiles can help in quantifying the dose – response relationships for different THC-effects, for instance to discriminate peripheral and central cannabinoid type 1 antagonists (Klumpers *et al.*, 2013b). Other applications of the dimensional scales could be in exploring the brain structures underlying different effects of THC (Atakan *et al.*, 2013), as well as examining the influence of genetic factors (i.e. polymorphisms) on the subjective effects of THC or cannabis (van Winkel and Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011). The dimensional quantification of cannabinoid effects can also help in exploring the relation between subjective effects to cannabis and clinical risk of psychosis, for instance by demonstrating that patients (or people at risk) show relatively

Table 3. Overview of different outcome measures

VAS item	LLOI	ULOI	% Responders	% Responders (0 mg)	% Responders (2 mg)	% Responders (4 mg)	% Responders (6 mg)	MCA: % inertia	PCA: comp. 1	PCA: comp. 2	Predictive value
Drowsy	36	61	62	13	21	37	52[1]	5.30	0.80	0.20	70.8
Calm	35	54	56	7	8	11	18	2.89	0.28	0.41	57.6
Feeble	37	56	52	7	17	30	45[1]	5.56	0.82	0.27	68.3
Muzzy	44	64	69	9	20	26	51	5.01	0.85	0.29	74.4
Clumsy	38	53	69	12	34	47	56[1]	5.25	0.80	0.30	71.5
Lethargic	35	62	66	7	9	16	20	0.60	-0.15	0.11	47.7
Contented	34	53	48	35	44	58	61	3.54	0.42	0.16	63.6
Tranquil	48	66	68	19	19	25	36	1.27	0.37	0.44	71.6
Mentally slow	42	64	69	9	22	36	54	5.53	0.84	0.23	75.8
Relaxed	46	66	53	11	15	21	34	2.13	0.52	0.12	72.4
Dreamy	38	61	64	5	23	41	55[1]	5.31	0.82	0.26	72.3
Incompetent	48	64	62	13	12	16	31	2.65	0.73	0.37	66.4
Happy	32	52	49	7	15	13	32	2.91	0.59	0.33	56.3
Amicable	48	68	47	20	26	20	27	0.59	0.47	0.09	47.6
Bored	37	62	34	6	6	14	18	1.26	0.68	0.04	53.8
Gregarious	47	69	50	16	17	15	30	1.34	0.68	0.38	61.8
Body	0	1	42	5	15	24	31[1]	3.71	0.26	0.69	55.9
Surroundings	0	1	40	1	15	25	37[1]	4.60	0.37	0.76	65.1
Time	0	1	63	4	27	48	57[1]	5.00	0.49	0.65	75.2
Reality	0	1	48	7	24	34	46[1]	4.63	0.37	0.77	67.6
Thoughts	0	1	74	7	39	63	66[1]	5.30	0.55	0.60	77.1
Colours	0	1	46	3	19	29	42[1]	3.76	0.27	0.69	63.9
Sound	0	1	49	3	20	31	39[1]	4.52	0.46	0.66	68.5
Voices	0	1	25	3	7	14	19	1.91	-0.01	0.84	54.2
Meaning	0	1	22	2	7	10	17[1]	1.71	0.09	0.76	53.8
Suspicious	0	1	21	4	7	12	16[1]	1.50	0.01	0.84	52.8
High	0	2	88	1	58	80	87[1]	4.63	0.58	0.46	83.6
Drowsy	0	3	58	7	30	40	61[1]	4.63	0.61	0.46	66.6
Anxious	0	1	35	4	11	19	30	2.95	0.29	0.78	56.8

[1]Significant dose – response relationship.

Table 4. Overview of suggested composite scale

Subscale perception
Time perception
Change in control of thoughts
Feeling high
Subscale relaxation
Feeling drowsy
Feeling muzzy, not having a clear head
Mental slowness
Feeling dreamy
Subscale dysphoria
Hearing voices
The idea that events, objects or people have a special meaning
Suspicious ideas or beliefs
Subscale appetite
Feelings of hunger
Feelings of appetite

strong "perception" effects, compared to the other effects of a cannabinoid challenge (Henquet *et al*., 2010).

The skewed distribution of VAS Bowdle is unfavourable for statistical analysis. The finding that a combination of items of the VAS Bond and Lader, which has an approximately normal distribution, explains most of the variation in effect is therefore important. The clear separation between items from VAS Bond and Lader and from VAS Bowdle that was seen with most methods is interesting. This could be caused by the differences in distribution that are characteristic for the scales, which is the result of (1) the use of two-sided versus one-sided scales and (2) the use of effects that are present and absent under "normal" circumstances (i.e. it is normal to have fluctuations in mood and alertness, but not in psychedelic effects). However, the separation could also be caused because the psychometric properties of the scales (i.e. what they measure) are different.

In summary, the current analysis provides experimental evidence that the subjective effects of THC in mild cannabis users have three main dimensions (consistent over a variety of statistical techniques). The main subjective effects of THC consist of feeling high and changes in perception. In addition, mental relaxation or dysphoric reactions can occur more or less independently. These findings correspond with previous descriptions of the subjective effects of THC and cannabis. The three dimensions can be used as the basis of an evidence-based composite scale (see Table 4, which could also include effects on hunger and appetite), to further explore and differentiate the involvement of endocannabinoid systems in health and disease and to quantify the subjective effects of THC and cannabis in clinical research. There seems to be a subset of individuals (even among occasional cannabis users) who respond to THC with dysphoric reactions and another small group of individuals who do not experience the typical "high" effects of THC. Further exploration of the genetic or psychological profiles of these individuals and the relation with subjective effect patterns could shed more light on the role of the cannabinoid system in health and (mental) disease.

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Declaration of interest statement

The authors declare no conflict of interest.

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